



## Sertaconazole in the treatment of mycoses: from dermatology to gynecology

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### Abstract

Sertaconazole is a pharmaceutical product in the form of a cream, gel, powder and solution for dermatological use and vaginal cream, tablets and ovules for gynecological use. It is marketed in 24 countries and registered in a further 22. The active ingredient is 2% sertaconazole nitrate. Sertaconazole nitrate is an azole antifungal agent, with notable antifungal activity. Its molecule has a highly lipophilic fragment. This is a review of the efficacy and safety of all pharmaceutical forms of sertaconazole in order to provide data on vaginal sertaconazole for marketing purposes. © 2000 International Federation of Gynecology and Obstetrics. All rights reserved.

**Keywords:** Sertaconazole; Mycoses; Dermatology

### 1. Dermatological clinical trials

The trials are classified as follows:

1. Comparative studies of sertaconazole 2% cream and sertaconazole 1% cream (Phase II).
2. Comparative studies of sertaconazole 2% cream and other imidazole derivative antifungal preparations (Phase III).
3. Efficacy and safety studies of sertaconazole solution compared to placebo.

4. Efficacy and safety studies of sertaconazole gel vs. placebo and ketoconazole.

#### *1.1. Phase II studies (comparison of sertaconazole 2% cream with sertaconazole 1% cream)*

These studies followed practically the same protocol. They included 20 patients randomized to two parallel groups. The age range of the patients was 18–70 years. Diagnosis was by clinical data, KOH microscopic examination and, where possible, microbiological culture. The duration of treatment was 28 days. A total of six visits were made during this trial; the sixth visit was to check for a recurrence of infection.

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(J. Torres).

Sertaconazole was administered topically in the form of a 2% or 1% cream. The cream was applied to the affected area twice a day, once in the morning and once at night, for 28 days (4 weeks).

Three studies were carried out in the following infections: pityriasis versicolor (Dr Nasarre), superficial mycoses caused by *Candida* (Prof Umberto) and cutaneous infections caused by dermatophytes (Dr Pedragosa).

In the study carried out on pityriasis versicolor [1], all patients were in good clinical condition at the end of treatment. This was also confirmed by microscopic examination and exploration with Wood's light. The results were similar for both treatments. No adverse reactions or signs of systemic tolerance were observed.

In candidiasis [2], the infection remitted in 19 out of 20 patients. The patient who was not cured belonged to the group treated with sertaconazole 2%. Prior to the trial, this patient had other mycotic infections in the same area which had not improved with the application of already marketed topical antimycotics. This patient was considered to suffer from a persistent mycosis, resistant to all topical antimycotic treatment. In the other patients all clinical signs and symptoms disappeared during the trial.

The signs studied were: erythema, desquamation, pruritus and maceration, all of them disappearing within 4 weeks, erythema being the last to disappear. There were no relapses of infection. A microbiologic and microscopic cure was obtained in both treatment groups.

No local or systemic adverse effects occurred during the trial in either of the patient groups. All haematologic and biochemical parameters remained within normal limits.

In dermatophytosis [3], all participating patients completed the trial appropriately. There were no missed visits or withdrawals. The efficacy of sertaconazole 1% and 2% cream was excellent, obtaining 100% cure in both groups. However, patients treated with the 2% cream improved sooner. All symptoms disappeared during the trial.

At the end of treatment (28 days) microscopic (KOH) cure and microbiologic (culture) cure were also reported in 100% of patients in both treat-

ment groups. From these results it can be concluded that the drug is effective against all dermatophytes isolated in the initial culture (*Trichophyton rubrum*, *Trichophyton mentagrophytes*, *Microsporum canis*, *Epidermophyton floccosum*, *Trichophyton schonleinii*).

No local or systemic adverse effects were observed during the trial. All chemical and clinical parameters remained within normal limits.

The results of these studies demonstrate the excellent efficacy of both preparations. However, sertaconazole 2% is superior, especially in infections caused by dermatophytes. Tolerability was excellent in both preparations.

#### 1.2. Phase III comparative trials between sertaconazole and other imidazole antifungal agents in cutaneous mycotic infections

These parallel group, double blind, multicentre trials included more than 1000 patients. They were performed in three countries: Spain, France and Germany.

The comparative study with sertaconazole and miconazole carried out by Alomar et al. in Spain [4], was a multicentre study. It included 631 patients with cutaneous infections caused by dermatophytes. The main objective of this trial was to study the clinical efficacy of sertaconazole 2% cream compared to miconazole 2% cream in the treatment of superficial cutaneous mycoses. The secondary objective was to confirm the safety and tolerability of sertaconazole which have been studied in previous phase I and II trials.

Patients of both sexes, aged between 18 and 70 years and with superficial cutaneous mycoses were considered eligible for the trial. A clinical diagnosis of dermatomycosis was confirmed by microscopic examination and culture tests. The patients randomly received the appropriate medication for a continuous period of 28 days; the cream was applied every 12 hours (twice a day).

A KOH direct microscopic examination was carried out on the third, fifth and sixth visit and was considered positive if hyphae or mycelia were observed.

The percentage of dropouts was much less than anticipated; therefore, patient recruitment was

stopped when 631 subjects had been included in the trial.

Of the 631 patients selected, 62 were withdrawn from the trial, which represents 10%, compared to the estimated 25% used to calculate group size. The sertaconazole group was made up of 295 patients and the miconazole group of 274 patients; therefore, the calculated number of patients was adequately covered.

Matching of the treatment groups was based on the baseline conditions of the patient. There were no statistically significant differences between any of these conditions. No appreciable differences were observed in the distribution of the different clinical forms of mycoses.

A comparison of the two groups showed a greater therapeutic efficacy for sertaconazole than miconazole. In the analysis of the actuarial curve of clinical improvement it was observed that, as from the fourth visit, patients treated with sertaconazole were cured sooner and in a higher proportion than those treated with miconazole, the difference being statistically significant ( $P > 0.05$ ). A comparison of the clinical efficacy of the two drugs on the different clinical forms showed a greater efficacy for sertaconazole. However, although the differences were considerable, they were not statistically significant.

Relapses occurred in 11.9% of patients treated with miconazole and in 4.4% in the group treated with sertaconazole.

In another Phase III trial carried out by Cevrant-Breton [4] in France, sertaconazole was compared with sulconazole.

This was a double blind, randomized, multicentre study in which 34 investigators participated. A total of 251 patients were included (147 men and 104 women) who had cutaneous candidiasis or dermatophytosis. They were treated with sertaconazole nitrate 2% cream or with sulconazole nitrate 1% cream. At the start of the study, 201 patients had a negative culture test (111 in the sertaconazole group and 90 in the sulconazole group). *Candida albicans* was isolated in 4.5% of the total number of patients, *Trichophyton rubrum* in 51.7% and *Trichophyton interdigitale* in 23.9%. A total of 68.7% of patients had clinical lesions in the toes,

24.9% in the groin and 26.8% in the feet. The treatment was applied once a day for 21 days.

At the end of treatment, 77.6% of patients treated with sertaconazole were mycologically cured, compared to 79.5% of patients treated with sulconazole. The difference was not statistically significant. Clinical cure was observed in 61.1% of patients treated with sertaconazole and in 47.6% of patients treated with sulconazole ( $P = 0.063$ ). On combining the number cures and number of improvements, the figure was 96.4% for sertaconazole and 93.4% for sulconazole (ns). There were eight relapses in the sertaconazole group and four in the sulconazole group.

These results indicate that both products have similar safety and efficacy.

In the clinical study carried out by Hagedorn [5] in Germany, sertaconazole was compared with clotrimazole.

This was a double blind, randomized, multicentre trial in which 14 investigators participated. A total of 173 patients (105 men and 68 women) diagnosed with cutaneous dermatophytosis, and treated with sertaconazole 2% cream or with clotrimazole 1% cream completed the study.

At the start of the study, 82 patients had a negative culture test (45 in the sertaconazole group and 37 in the clotrimazole group). In 16 patients *Candida albicans* was isolated, and in 34, *Trichophyton rubrum*. A total of 136 patients had clinical lesions in the feet and 25 in the groin. Treatment was applied twice a day for a minimum of 14 and a maximum of 28 days.

At the end of treatment, 49% of the patients treated with sertaconazole who had a negative culture test at the start of treatment were mycologically cured, compared to patients treated with clotrimazole. The difference was not statistically significant.

A clinical cure of the cutaneous lesions after 14 days of treatment was observed in 32% of patients treated with sertaconazole and 21% of patients treated with clotrimazole. Subjective discomfort disappeared after 14 days of treatment in 77% of patients treated with sertaconazole and in 75% treated with clotrimazole. Notable differences between the groups were not observed.

These results indicate that both drugs have similar safety and efficacy profiles.

The comparative studies between sertaconazole and miconazole, and sulconazole and clotrimazole, therefore, show similar results as regards safety and efficacy. Sertaconazole demonstrated superior efficacy, especially compared to miconazole.

In dermatological practice, it is advisable and sometimes essential to have other antifungal pharmaceutical forms available. Due to the in vivo and in vitro spectrum of activity of sertaconazole and its tolerability, other pharmaceutical forms of this drug may be employed, as has been demonstrated in clinical trials and clinical experience with gel, solution and powder preparations.

The solution is a pharmaceutical form commonly used in dermatology. It is mainly used in lesions of hairy or moist areas and in infections where treatment needs to be applied over large body surfaces areas. This dosage form also prevents maceration, which sometimes occurs with creams or ointments and overcomes the cosmetic drawbacks of greasy preparations. Applying an unsuitable topical preparation is often the cause of treatment failure in mycosis occurring in hairy areas.

#### *1.3. Efficacy and safety studies of sertaconazole solution compared to placebo*

In a double blind, parallel group, randomized, placebo controlled clinical trial carried out by Crespo [6], the efficacy and safety of sertaconazole solution was studied in 60 patients with pityriasis versicolor confirmed by KOH microscopic examination and exploration with Wood's light. The patients received sertaconazole 2% solution, twice a day for 28 days. Evolution of the disease was evaluated clinically and microscopically (optical and fluorescence).

Twice the amount of clinical cures were observed with the sertaconazole group than the placebo group ( $P < 0.001$ ). A greater number of negative results in the microscopic and fluorescence tests were found with sertaconazole.

The survival analysis (actuarial method) revealed that patients treated with sertaconazole

reached a more favorable clinical situation sooner than the placebo treated patients.

Consequently, because of its excellent efficacy and safety profile as well as its ease of application, sertaconazole 2% solution represents an important advance in the topical therapy of this disease.

Topical powder is preferred for treatment of skin fold areas. In addition to its active components a powder formulation also has drying properties that prevent maceration. These properties are especially important in the treatment of mycoses because moisture and maceration are pathogenic factors and sustain infection.

The main objective of antifungal gel preparations is to eliminate fungi in hairy areas. Therefore, its main indication is in diseases of the scalp that require antimycotic treatment.

#### *1.4. Efficacy and safety studies on sertaconazole gel vs. placebo and ketoconazole*

Alsina and Zemba [7] performed a preliminary therapeutic trial on the efficacy of sertaconazole in the treatment of seborrheic dermatitis of the scalp in 15 adult patients of both sexes. The trial was a double blind, randomized design, to compare the efficacy and tolerability of sertaconazole 2% gel with a placebo. The topical gel was applied once a day every 3 days for 4 weeks. It is noteworthy that in the patients treated with sertaconazole, there was an overall statistically significant decrease in the severity of the clinical signs of pruritus and desquamation. It is also noteworthy that in the same patients, there was an overall statistically significant decrease in dermatitis.

Likewise, the evolution of the patients who initially presented with severe disease is particularly interesting. In the two patients treated with placebo, the clinical signs persisted. On the other hand, patients treated with sertaconazole improved considerably.

In another study carried out by Szlachcic [8] the efficacy and safety of sertaconazole 2% gel was compared to ketoconazole 2% gel in the treatment of seborrheic dermatitis of the scalp. It was a double blind, randomized, parallel group design.

Sixty patients of both sexes were included. The duration of treatment was 28 days.

This study demonstrated that treatment of seborrheic dermatitis with sertaconazole for 4 weeks produced a considerable improvement of symptoms, and was clinically superior to that obtained with ketoconazole. None of the patients abandoned the trial due to adverse effects.

These results may be considered as clinically relevant, as they demonstrate the efficacy and safety of sertaconazole 2% gel compared to a drug considered to be an established reference standard.

### 1.5. Conclusions

In the field of dermatology, clinical and pharmacological studies have demonstrated that sertaconazole is very well tolerated by the skin. Epicutaneous tests have shown that sertaconazole does not have a sensitization effect on the skin.

Sertaconazole is not absorbed systemically when applied to the skin as a cream. Nevertheless, it penetrates the stratum corneum.

The clinical efficacy of sertaconazole has been established through comparative controlled trials which have included at least 1000 patients with cutaneous mycoses (candidiasis, dermatophytosis and pityriasis versicolor). These studies have demonstrated that sertaconazole has similar or even superior safety and efficacy to other imidazole antifungal agents, such as miconazole, sulconazole, clotrimazole and ketoconazole.

In addition, the wide range of pharmaceutical forms (cream, solution, powder and gel) provide dermatologists with the opportunity to select the most appropriate form in order to prevent treatment failure due to an unsuitable topical preparation.

## 2. Sertaconazole in gynecology

Vulvovaginal mycoses are the most common reason for visits to the gynecologist, and those caused by *Candida* are on the increase in many developed countries [9–11]. The incidence of vaginal candidiasis could be 20% in women with

normal sexual activity and is clinically characterized by vulvar pruritus, vaginal secretion with or without frank vaginitis, leukorrhea, vulvar erythema and maceration amongst other symptoms. The most frequent causative microorganism is *Candida albicans*, isolated in more than 80% of samples, followed by *Candida glabrata* and other *Candida* species. Thanks to the work by Wilkinson (1849), the first person to establish a link between a fungus and vaginal infection, treatment with gentian violet was started (1935). This was subsequently replaced by nystatin (1955) which was the treatment of choice until the advent of imidazole agents in the 1970s. At the present time, this class of drugs is commonly used in this type of infection due to their greater efficacy, short treatment regimens, and ease of administration [12]. However the low response to treatment of infections caused by *C. glabrata*, as well as resistant *C. albicans* strains in immunodepressed patients, presents an important therapeutical problem [13] and continued research into new, useful drugs is recommended.

Furthermore, administration regimens need to be simplified as they play a vital role in treatment efficacy and prevention of relapses.

Sertaconazole is a new synthetic antimycotic agent with a broad spectrum of action. It is fast acting and very effective especially against yeasts of the *Candida* genus. Results obtained in vitro have been confirmed in vivo, using animal models of vaginal infection, and demonstrate the greater activity of sertaconazole over other standard antimycotic agents [14]. All this justifies the initiation of clinical investigation into this drug.

Clinical investigation into new formulations for vaginal application had the following objectives:

- To study the tolerability of pharmaceutical formulations administered by vaginal route, determining the systemic absorption of the drug and reporting adverse effects.
- To determine the appropriate dose, confirm the efficacy of the different formulations (pessaries and sustained release vaginal ovule) and to determine the efficacy of single dose administration.

- To determine efficacy in conditions similar to those in routine clinical practice through multicentre, randomized, controlled (miconazole, econazole, clotrimazole) clinical trials, with clinical and mycological determinations.

These trials have been carried out according to current legislation on clinical trials and complying to appropriate ethical principals.

In this review five trials are analyzed:

- A Phase I trial in 12 healthy volunteers to determine the safety of sertaconazole 2% cream (single and repeated doses) and vaginal tablet (single dose).
- A dose-finding study for a vaginal tablet in 59 patients with vulvovaginal candidiasis.
- Two Phase III multicentre, controlled, clinical trials in 1038 patients with vulvovaginal candidiasis with vaginal tablet and vaginal cream 2%.
- A Phase III clinical trial with 300 mg vaginal ovule in 369 patients providing supplementary data on safety, efficacy and tolerability.

This review aims to analyze the results of these trials and to compare them with those reported in the literature for other drugs in this indication. Likewise, the design and methodology study population and sample size will be critically assessed.

### 3. Gynecological investigation

#### 3.1. Characteristics of the study population

The objective of the study in healthy volunteers was to determine local and systemic tolerability of the application of vaginal dosage forms, to determine the persistence of the drug in vaginal secretion and to quantitatively determine drug concentrations in the blood and urine.

The trial included 12 women aged between 21 and 35 years, with an average weight of 57.3 kg (49–64 kg) and normal gynecological examination. The dosage forms studied were a 500-mg

tablet and 2% cream, the latter applied both as a single dose and as repeated doses.

#### 3.2. Methodology

This was a double blind, cross-over, controlled trial. The excipients of the active formulations of the vaginal tablets and the vaginal cream were used as controls. The trial was sub-divided into three stages, which were well established and defined in the protocol: single dose cream, repeated dose cream and single dose vaginal tablet. The stages corresponded to the patient's menstrual cycle. Between the different stages and application sequences (active ingredient and placebo) wash out periods were inserted that ranged between 3 and 18 days. These appeared to adequately eliminate any interference or possible carry-over effects.

Objective and subjective variables were analyzed to determine the drug's safety and tolerability administered by the two different routes. During the follow-up, the following were carried out: a questionnaire (check-list) on local and systemic adverse events; a 10 point visual analogue scale (VAS-100 mm) was completed by the volunteers, in which the tolerability of treatment was assessed; questionnaires on the effects experienced as symptoms (18 items); recording of vital signs (systolic and diastolic blood pressure, heart rate and body temperature); and an electrocardiogram examination and blood and urine tests. A thorough gynecological examination was also carried out which included tests on the vaginal mucosa, vaginal discharge, pH, Papanicolaou test and colposcopy (this examination was always carried out by the same gynecologist, to ensure maximum reproducibility of the results).

#### 3.3. Results, comments and discussion

The selection criteria established in the protocol are clear, and although strict, are appropriate for a Phase I study.

The method of administration of the drug was well established. It was effective and uniform due to the use of disposable applicators and the fact

that the volunteers were properly instructed. At the end of the trial the participants had applied a total of 2.1 g of sertaconazole (80 g of 2% cream and one 500-mg tablet).

That trial was approved by the Ethics Committee on Clinical Research of the hospital and by the Health Authorities. Information for the subjects and signed informed consent forms were provided. Therefore, the study was conducted according to internationally accepted ethical recommendations. The statistical analysis of the data was carried out by an independent organization (Centro de Calculo del al Universidad Autónoma de Barcelona (U.A.B.), with the collaboration of the Phase I Unit of the Hospital de la Santa Cruz y San Pablo de Barcelona).

Determination of the drug in urine, vaginal discharge and plasma was performed by HPLC with UV detection. This method can determine sertaconazole concentrations of 20 ng/ml (in plasma), 25 ng/ml (in urine) and 80 ng/ml (in vaginal secretion). The procedure, processing of samples, chromatographic conditions, reference standards, reagents and equipment were established by well-defined protocols.

The analysis of plasma samples after the application of the cream (single and repeated doses) and insertion of the tablet did not reveal sertaconazole concentrations under the test conditions used. The analysis of urine samples, revealed low concentrations of the drug ( $\bar{x}$  = 0.27% of the tablet dose); however, since these were random findings taken at different times, this may have been due to contamination of the vaginal area, inevitable with this form of administration. This is in keeping with the pharmaceutical formulation of vaginal tablets, which contains excipients that provide bioadhesivity to facilitate retention of the tablets in the vaginal mucosa. It is difficult to compare these findings with those reported in the literature because the trials carried out on this class of drugs and in this indication are not standardized. From published articles, variability in the techniques, dose range and method of administrations was observed. Nevertheless, it is worth pointing out that systemic absorption was reported in some studies [15,16], in contrast to the findings in this study with sertaconazole.

In gynecological examinations carried out on the volunteers after each treatment stage, no significant changes in vaginal mucosa or discharge, volume of discharge or the pH were observed. The changes that occurred were adaptive changes of the mucosa due to the menstrual cycle. Cytological tests did not show any abnormalities. The laboratory test results (plasma and urine) were within the normal physiological range both for the placebo and sertaconazole. Vital signs were also normal, the fluctuations being typical circadian variations. No clinically relevant differences between sertaconazole and placebo were detected in the visual analogue scale results.

As regards the safety of the drug, no relevant adverse events were reported and the number of effects experienced as symptoms (12 for placebo and 10 for sertaconazole) was very low, and only occurred with the cream formulation, not being reported with the tablet. These symptoms were mild and disappeared spontaneously (headache and drowsiness). The methodology and criteria for the determination of adverse events was, therefore, appropriate. These methods were well structured and had good detection and discrimination capacity [17].

The overall review of the safety data suggests that the drug, both as a vaginal tablet and as a cream, is not absorbed systemically, is generally safe and is well tolerated:

- The visual analogue scale did not reveal any differences between sertaconazole administered in any of the pharmaceutical forms and the placebo.
- Hardly any effects experienced as symptoms were reported and those reported (only with the cream) also occurred with the placebo. Therefore, it is very likely that the cause was environmental and not attributable to the drug.
- Biochemical and haemodynamic parameters were within the normal range.
- No differences were observed between the volunteers who received sertaconazole and those who received the placebo as regards the state of the vaginal mucosa, vaginal discharge and pH, and results of the colposcopy.

- Concentrations of sertaconazole were not found in any of the samples analyzed in any of the volunteers; therefore, if traces of the drug were present these would be below the detection level of the technique used. The low concentrations found in the urine were variable and erratic.

The possible therapeutic potential, which depends on the drug concentration reached in vaginal secretion, only requires clinical confirmation from studies in patients with candidiasis. The levels reached with both formulations are high and persistent thus justifying the single dose application. The fact that the 500-mg vaginal tablet reaches much higher concentrations than the cream at both 24 and 28 h is noteworthy. Drug concentrations in the vagina, both with the cream and the tablet, appear to be much higher than the minimum inhibitory concentrations (MIC) and fungicidal concentrations obtained in in vitro studies for sertaconazole against *C. albicans*, *C. glabrata* and other non-*Candida albicans*. These data indicate that from a practical point of view, the single dose treatment could be considered as being the same as at least a 3-day treatment and it has the added advantage of avoiding poor compliance of the patient which is a basic cause of treatment failure in this type of treatment [18].

The design and performance of the study, therefore, is that of a Phase I study, initial development of the clinical phase. It adequately determines the clinical safety and effects of the drug. Healthy volunteers rather than patients were used in the study, in accordance with international recommendations on clinical trials. This avoids modifying factors due to the presence of disease, possible ethical problems or deviations from the protocol due to the need for concomitant medication which could effect the evaluation [19]. The majority of international recommendations concern systemic drugs and there are very few guidelines geared towards the evaluation of objective and subjective tolerability of new vaginal antimycotic agents. Therefore, the gynecological examinations and different tests carried out in this study provide a good knowledge of local tolerability, whilst the EES and VAS questionnaires on

adverse effects provide information on general drug acceptance and safety. Monitoring of drug concentrations in plasma and vaginal secretion help to establish the pharmacodynamics of the drug.

#### 4. Gynecological clinical trials

##### 4.1. Clinical investigation

The results of clinical trials performed for the registration of vaginal pharmaceutical forms of sertaconazole (vaginal cream, tablet and ovule) were evaluated. A total of 1109 subjects were included in these trials and 585 women were treated with sertaconazole in different vaginal dosage forms. This number increases to more than 1400 if we add patients included in trials with other vaginal dosage forms in which approximately 800 women received sertaconazole in one form or another.

All the trials evaluated complied with prevailing regulations on clinical trials in that they were approved by the respective Ethics Committees on Clinical Research and the Directorate General of Pharmacy and Health Care Products. They generally respect the ethical and scientific standards recommended by current regulation.

The single center, double blind, randomized, Phase II trial with two dose levels performed in Spain included 59 patients with vulvovaginitis caused by *Candida albicans*. The patients were treated with a single dose vaginal tablet. The efficacy was determined based on clinical and microbiologic criteria.

Two pragmatic clinical trials were performed involving more than one thousand patients. In the first one a total of 582 patients with vulvovaginal candidiasis (288 assigned to the sertaconazole group) were included in a multicentre, randomized, controlled, parallel group trial. The study was carried out at 14 centers (national hospitals and primary health care centers). The second trial was a multicentre clinical trial involving 456 patients diagnosed with microbiologically confirmed vulvovaginal candidiasis, 226 of whom received sertaconazole. A multicentre trial was

performed in France with 369 patients and provides supplementary data on efficacy, general safety local tolerability.

The formulations and doses tested were 300 mg sustained release vaginal ovule, 500-mg vaginal tablet (both single dose) and 2% vaginal cream in repeated applications for 7 days. Clotrimazole (500-mg vaginal tablets) and miconazole 2% cream were used as the reference compounds. The study used 300-mg vaginal ovules and econazole as the control drug (Gyno-Pévaryl® LP 150 mg).

The design of the trial was appropriate (double blind, randomized, controlled, parallel groups). The efficacy criteria established were clear and objective (clinical, culture and microscopic examinations). The procedure and intervals between the control tests (visits, mycological evaluation) were adequate and coherent.

The safety evaluation carried out using structured methods (check-list) and non structured methods (open questions) to detect adverse events, enabled information on the drug's safety profile to be reliably obtained. The study used algorithms to determine causality, and complied with criteria of Good Clinical Practice and Spanish legislation concerning clinical trials.

#### 4.2. Evaluation of individual studies

##### 4.2.1. Phase II trial

This was a trial to determine the efficacy and safety of a single dose vaginal tablet of sertaconazole in patients with vulvovaginal candidiasis.

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**4.2.1.1. Patients.** A total of 59 patients with vulvovaginal candidiasis (29 in the sertaconazole 300-mg group and 30 in the sertaconazole 500-mg group). Diagnosis was clinical (genital pruritus and secretion with suspicion of candidiasis) and confirmed mycologically (microscopic examination and culture test). Three patients were excluded from the trial (negative baseline culture test and concomitant disease). Two patients (sertaconazole 300 mg group) were withdrawn

due to poor evolution and one patient was lost to follow up. With the exception of height, baseline data were comparable in the two groups. The Quetelet index was calculated to rule out differences in obesity, the two groups were comparable.

Clinical assessment, symptomatology, direct microscopic examination and culture test were performed at the start of the trial and at day 7 and day 14.

**4.2.1.2. Therapeutic efficacy.** Sertaconazole in the form of vaginal tablet achieved total clinical cure in half of the patients after 7 days. This increased to 68% when assessed after 14 days. After 7 days of treatment the clinical cure rate was notably higher with the 500-mg tablet (57.1%) than with the 300-mg tablet (39.3%), and was also higher when evaluated at day 14 (71.4% vs. 64.3%). When considering patients with complete or advanced clinical cure the results with the 500-mg tablet were still better (89% vs. 78%).

On day 7, the results of the microscopic examination were negative in 87.5% of patients treated with sertaconazole and on day 14 in 82.1% of patients. The 500-mg dose continued to achieve better results both in the evaluation on day 7 (89.3%) and that on day 14 (85.7%) than those of the 300 mg tablet (85.7% and 78.6%, respectively). Both doses achieved similar mycological eradication rates on day 7 (86%), the 500-mg dose being superior on day 14 (89.3% vs. 82.1%).

**4.2.1.3. Safety.** No systemic adverse events were reported in any of the patients. Only mild local adverse events (pruritus, leukorrhea or erythema) were reported in four patients (two patients in the sertaconazole 500-mg group). It is difficult to ascertain whether the symptoms were drug-related, as they are typical of candidiasis.

All the laboratory parameters (biochemical and hematological) were within normal limits, with no alterations being observed after exposure to the drug.

The tolerability of the formulation was considered satisfactory by 85% of patients. The 500-mg (93.3%) formulation was classified as satisfactory by more patients than the 300-mg (75.9%) formulation.

**4.2.1.4. Design and quality of the trial.** The design of this randomized, double-blind, parallel group trial is appropriate to obtain the proposed objectives. The methods for the evaluation of efficacy are objective (microscopic and culture), and the clinical evaluation is suitable.

The patient selection criteria are the usual ones for clinical trials to determine the efficacy of new antifungal agents and take into account patient age, clinical diagnosis, mycological confirmation, concomitant treatment and intercurrent diseases.

Statistical analysis is clearly explained in the protocol and was carried out by specialized personnel at the Department of Epidemiology, Instituto Municipal de Investigación Médica, Barcelona, which is not connected to the Sponsor company.

Safety was determined by means of a structured method (check-list) which enabled a thorough knowledge of the product safety profile to be gained. Exhaustive laboratory tests (hematology and biochemistry) were also performed. The Karch–Lasagna algorithm was used to determine causality.

Ethical aspects were appropriately considered and the protocol included a patient's information sheet, and signed informed consent was obtained. Furthermore, reference is made to authorization by the Ethics Committee and Directorate General de Pharmacy and Health Care Products.

#### 4.2.2. Phase III Trial

This is a Phase III clinical trial to compare the efficacy and safety of a single dose 500-mg sertaconazole vaginal tablet with the same dose of clotrimazole in patients with vulvovaginal candidiasis.

Departments of Gynecology and Obstetrics. Multicentre, clinical trial in Spain.

**4.2.2.1. Patients.** A total of 582 patients ( $33 \pm 9$  years) were included in this multicentre, randomized, double-blind, parallel group, controlled, clinical trial, 49.5% of whom received sertaconazole (288) and the remainder clotrimazole (294) both drugs in the form of a 500-mg vaginal tablet.

The ambulatory patients received treatment at hospitals and primary health care centers or family planning clinics.

The clinical diagnosis was mycologically confirmed (microscopy and culture). Reasons for patient withdrawals from the trials were loss to follow up (11.6% in the clotrimazole group and 10.4% in the sertaconazole group) and poor evolution (25.2% in the clotrimazole group and 23.6% in the sertaconazole group). Other reasons for dropouts or withdrawals were adverse events, intercurrent diseases, negative baseline culture or recurrences due to sexual intercourse. There were no significant differences in the number of withdrawals between the two treatment groups, although there were more withdrawals due to poor evolution in the clotrimazole group. Both groups were comparable regarding the initial characteristics studied.

The trial consisted of three visits (day 0, 7 and 14) during which evaluation of clinical signs and symptoms (vulvar, vaginal or cervical) examination of the vaginal discharge, microscopic tests (fornix vaginae) and culture tests were carried out.

**4.2.2.2. Therapeutic efficacy.** The sertaconazole group showed a better clinical response after 7 days (36.4%) than the clotrimazole group (30.9%). Approximately 81% of patients treated with either sertaconazole or clotrimazole had complete clinical cure at the day 14 visit. Sertaconazole was slightly superior to clotrimazole in the improvement of vulvar and cervical pruritus and erythema, but the difference was not statistical significance.

The microscopic examination carried out on day 7 revealed more positive fornix vaginae tests in the clotrimazole group, although the difference was not statistically significant (15.5% vs. 21.1%). Less than 5% of patients had a positive microscopic examination on day 14.

Mycological eradication was obtained on day 7 in 70–72% of patients treated with sertaconazole whilst this was achieved on day 14 in 90% of patients treated with clotrimazole (11.6% and 7.7% of positive cultures, respectively).

**4.2.2.3. Safety.** These results demonstrate a good safety profile for both products. The local adverse events reported were mainly mild or moderate and were difficult to differentiate from the associated symptomatology. The most frequent adverse events in both treatments were pruritus and erythema. Burning, pain, increased sensitivity, edema, redness, leukorrhea and maceration were also reported.

Very few systemic adverse events were reported (headache, drowsiness, nausea, constipation, diarrhea). None of these were severe and none of the investigators considered them to be treatment-related.

Tolerability of the sertaconazole formulation was considered to be very satisfactory by 88% of investigators and 91% of patients. Similar results were found with clotrimazole.

**4.2.2.4. Design and quality of the trial.** The study design was that of a pragmatic trial which aimed to simulate conditions similar to those in routine clinical practice without precluding blinding and randomization, which are important in avoiding bias.

Clotrimazole is a good reference compound as it was the first azole antifungal agent to be introduced in clinical practice for short term treatment and is very effective in this indication [20,21]. After the administration of a 500-mg dose, inhibitory levels are reached in vaginal secretion for 2–3 days and the drug is safe in this dosage form [22]. It is, therefore, considered a good reference compound for comparative studies.

The criteria for evaluation of efficacy are objective (microscopic and culture), and there is adequate clinical evaluation.

The calculation of the sample size is justified and suitable for the study objectives. The patient selection criteria are those normally used in clinical trials in this disease. Data analysis, statistical tests, and the power of the trial are appropriately described and were carried out at the Instituto Municipal de Investigación Médica, Barcelona.

As with the previous study, safety was evaluated by means of a questionnaire to determine adverse events. In this questionnaire the start, duration, severity and relation to study drug of

the adverse events are reported, using a causality algorithm.

The protocol provides a patient information sheet, a signed informed consent form and refers to approvals by the Ethics Committee and the Directorate General for Pharmacy and Health Care Products (no. 90/163. 1–14).

#### **4.2.3. Phase III trial**

This is a clinical trial to compare the therapeutic efficacy of a sertaconazole 2% vaginal cream with a miconazole 2% vaginal cream in patients with vulvovaginal candidiasis.

Departments of Gynecology and Obstetrics. Multicentre, clinical trial in Spain.

**4.2.3.1. Patients.** This is a double blind, controlled clinical trial in 456 patients diagnosed with vulvovaginal candidiasis confirmed by vaginal secretion culture test (226 assigned to the sertaconazole group). Both sertaconazole and miconazole were applied in the form of a vaginal cream once a day for one week. Clinical, microscopic and microbiological tests were carried out after 3 days, 14 days and at the end of treatment.

There were no differences between the treatment groups at the start of the study (age, weight, height, concomitant diseases, contraceptive methods, additional treatment). One patient in the sertaconazole group and six patients in the miconazole group were excluded from the trial due to non-compliance with the inclusion criteria (five patients had received antibiotic treatment, one had intercurrent disease and one had received inappropriate topical treatment). The baseline culture test was negative in 10 patients in the sertaconazole group and in 11 patients in the miconazole group. These patients were excluded from the evaluation of efficacy.

**4.2.3.2. Therapeutic efficacy.** The mycologic cure rate 3 days after the end of treatment was 83.3% for sertaconazole and 84.1% for miconazole. The percentage of patients who achieved a clinical and mycologic cure was 44.1% for sertaconazole and 41.8% for miconazole. Similar results for both treatments were observed for recurrence rate, this being less than 3%.

**4.2.3.3. Safety.** Local tolerability was satisfactory for both groups in 90% of patients. Patients treated with sertaconazole reported less adverse events (7.9%) than those treated with miconazole (11.3%); this difference was not statistically significant.

There were no changes in hematological and biochemical parameters, nor in liver function that could suggest systemic action of the two drugs.

**4.2.3.4. Design and quality of the study.** Objective diagnostic criteria (culture test, direct microscopic examination) were used. The design (controlled, randomized double-blind) and the performance of the trial were suitable to obtain the desired objectives. Efficacy was determined by suitable, structured methods and causality of adverse events by the Karch–Lasagna algorithm.

The sample size was adequately calculated and the number of patients included in the trial complied to the initial statistical requirements. The statistical analysis was also carried out by an independent organization, Clinical Pharmacology Department of the Instituto Catalán de Farmacología (U.A.B. Barcelona).

The control drug, miconazole, and the dosage form and administration were suitable as the efficacy (51–88%) and safety of this drug have been demonstrated in clinical trials [23].

Patients were informed of the nature of the trial by the investigator, and signed informed consent was obtained before a witness. The trial was approved by both the Ethics Committees of the participating centers and the Health Authorities (N0. 91/67.1–8).

#### 4.2.4. Multicentre study

This is a study to compare the efficacy and safety of sertaconazole with econazole (Gyno-Pévaryl®) in the form of sustained release vaginal ovules in the treatment of vaginal candidiasis.

Departments of Gynecology and Obstetrics. Multicentre clinical trial in France.

**4.2.4.1. Patients.** This was a multicentre, double blind, parallel group, randomized, controlled, Phase III trial. Inclusion criteria were women with vulvovaginal candidiasis treated on an out-

patient basis and with positive baseline culture test. The trial consisted of a maximum of four visits (days 0, 7, 14, 37 or 44) at which a physical and gynecological examination and a microbiological test were carried out. The patients could receive a second ovule if cure was not achieved, and a clinical and mycological examination was carried out the following week (day 14). All patients were evaluated 5 weeks after administration of the last ovule (day 37 or 44). Mycological, clinical and safety parameters were evaluated.

A total of 369 patients were included ( $32.0 \pm 0.55$  years) 83 of whom (49.6%) were assigned to the sertaconazole group and 186 (50.4%) to the econazole group. Negative baseline culture tests were obtained in 59 patients (33 in the sertaconazole group and 26 in the econazole group). Efficacy was evaluated in 310 patients (150 in the sertaconazole group and 160 in the econazole group); *C. albicans* being isolated as the causative agent in 95% of patients. Both groups were comparable as regards demographic, clinical and therapeutic characteristics except for dysuria and antibiotic treatment. These differences did not affect the evaluation of efficacy and safety.

Eight patients were lost to follow up (five in the sertaconazole group and three in the econazole group), one patient (econazole) abandoned for reasons not connected with the trial, and 11 patients abandoned the trial due to reasons related to the protocol (two due to cure and three due to inefficacy in the sertaconazole group; two due to cure and five for inefficacy in the econazole group). None of the patients abandoned due to adverse events.

**4.2.4.2. Therapeutic efficacy.** The microscopic examination carried out at the day 7 visit was negative in approximately 90% of patients treated with sertaconazole or econazole. A negative culture test was obtained in 70.8% of patients after administration of one sertaconazole vaginal ovule, while a negative culture test was obtained in 64.7% of patients in the econazole group (ns). The clinical cure rate in patients treated with sertaconazole was 63.8% and 60.5% in those treated with econazole.

Fifty patients in the sertaconazole group and 56 patients in the econazole group received a second vaginal ovule, and the microscopic examination was negative in 93.8% and 94.6% of the patients, respectively. A mycologic cure occurred in 77.1% (sertaconazole) and 83.6% of patients (econazole). The clinical cure rate was 71.4% in patients treated with sertaconazole and 73.2% in those treated with econazole.

The direct microscopic examination carried out one month after the end of treatment was negative in 76.6% of patients in the sertaconazole group and in 74.5% of patients in the econazole group. Culture tests were negative in 65.4% of patients who received sertaconazole and in only 58.9% of those who received econazole. The clinical cure rate for both drugs was 65%. There was a higher cure rate in women who received a single sertaconazole ovule (67.4%) compared to those who had received a single econazole ovule (59.0%). The number of relapses in patients treated with sertaconazole was less than those treated with econazole ( $P < 0.05$ ).

Overall evaluation of efficacy was very satisfactory as 94% of patients treated with one or the other drug achieved cure at some time during the study. These good results were supported by the mycological efficacy (80%). The investigator considered that treatment efficacy was excellent or good in 78.8% of patients treated with sertaconazole and 76.9% in patients treated with econazole. Efficacy was considered poor in only 8.2% of patients in the sertaconazole group and in 12.2% of patients in the econazole group.

**4.2.4.3. Safety.** Treatment tolerability was considered favorable for both drugs, both by the patient and the investigators.

Fewer local adverse events were reported in the sertaconazole group (8.7%) than in the econazole group (13.4%); the difference not reaching statistical difference. The most frequent adverse events were pruritus and burning, probably caused by the antifungal activity of the drugs. Systemic adverse events (pelvic pain, migraine, nausea, vomiting, generalized pruritus, diarrhea and gastric discomfort) were reported in only six patients, and none were considered as having a definite causal relationship with the study treatment.

**4.2.4.4. Design and quality of the study.** This clinical trial is included in this review as it provides data on efficacy, local tolerability and general safety which are useful to better determine the safety profile of the product administered by this route. The study was carried out by a pharmaceutical company who have marketed the product in France. More than 79 investigators participated at 50 centers. The trial was performed according to Good Clinical Practice standards and included 369 patients.

The choice of reference compound (econazole) was due to the fact that this drug is extensively used in France in this indication and as a single dose regimen. The efficacy of econazole reported in this trial although poor corresponds to that reported by other authors.

The inclusion and exclusion criteria were such as to simulate routine clinical practice conditions in as much as possible. The population had a normal range of risk factors.

#### **4.2.5. Benefit / risk ratio of intravaginal sertaconazole**

The clinical trials, when carried out satisfactorily, establish the benefit–risk ratio of the product with this administration route. This assertion is based on:

##### **(a) Design of trials:**

- Explanatory and pragmatic trials of randomized, double blind, parallel group or cross over design.
- Multicentre trials. The three Phase III trials involved several centers covering a wide geographical area.
- Controlled trials using reference compounds with demonstrated efficacy (clotrimazole, miconazole and econazole).

##### **(b) Criteria:**

- Well defined inclusion and exclusion criteria and were those usually recommended in the evaluation of new drugs in the treatment of vaginal infections.
- Evaluation: microscopy, culture, clinical signs and symptoms.

- Tolerability and safety: check-list, open questions on adverse events, effects experienced as symptoms, visual analogue scales, blood and urine tests.

(c) Study population:

- Healthy volunteers and patients with vulvo-vaginal candidiasis.
- Age, localization, evolution time and treatment representative of routine clinical practice.

Overall, the results of these trials appear to be valid and establish a well correlated therapeutic efficacy microscopically, microbiologically and clinically. Sertaconazole administered by all the vaginal presentations (cream, tablet or ovule) was as effective as the reference compounds and for some parameters (clinical, relapse) it was superior. In all controlled trials favorable trends for sertaconazole were observed, although they did not reach statistical significance. It is of note that sertaconazole demonstrated efficacy in patients with diverse characteristics (18-65 years; vulvar, vaginal or vulvovaginal localization of infection; *C. albicans*, *non-albicans*). This efficacy was evidenced in the first few days of treatment by a significant reduction in clinical signs and symptoms and the negative results of the first microbiological tests. Efficacy is also demonstrated by the continued negative results, and by the low rate of relapses (after 7, 14 or 28 days) after treatment. This fast rate of action is also conducive to the patient's acceptance of the treatment which is essential for compliance to the treatment regimen.

Administration by the vaginal route has been demonstrated as safe. There were no withdrawals due to adverse reactions in patients treated with sertaconazole in any of the trials, irrespective of the dosage form. Alterations in blood tests were not observed either. General adverse events were unspecific and a causal relation to the drug was not established in any of the subjects. The local tolerability profile was satisfactory and very few local effects, usually pruritus, burning or erythema, were reported. Although statistically sig-

nificant differences were not observed in two of the studies (single dose or cream applied for 7 days), fewer local adverse events occurred with sertaconazole compared with other drugs, this difference being 4%. This tolerability and safety profile encourages treatment compliance and therefore a good response to therapy ultimately lowering cost of treatment.

In summary, sertaconazole by this administration route is an attractive treatment alternative since it offers safe, efficacious treatment regimens which in some aspects are better than those of other drugs.

#### 4.3. Overall analysis

##### 4.3.1. Efficacy

A total of 1109 women (healthy volunteers and patients) participated in the clinical development of cream, tablet and ovule formulations, 585 of whom received sertaconazole in one form or another. Efficacy data are also provided from a clinical trial conducted in France with an intravaginal formulation (ovule) that involved 369 patients, 183 of whom received sertaconazole.

The control group received standard active treatments which ensured reliability in the comparison of results.

Patients with comparable characteristics had been selected in order to ensure reproducibility of efficacy and safety data.

The Phase II study corroborates the results of the drug's activity in pre-clinical studies. Sertaconazole as a single dose vaginal tablet has high efficacy and an eradication rate of 80% and 90% after 7 and 14 days. It also resolves signs and symptoms of candidiasis infection in 90% of patients with vulvar and 70% of patients with vaginal involvement. Despite the absence of statistically significant differences between the two doses tested, the 500-mg dose shows slight superiority — complete clinical cure (71% vs. 64%), microscopic cure (84% vs. 78%) and microbiologic cure (89% vs. 82%). Furthermore, withdrawals due to poor evolution occurred in the 300-mg group. This study, therefore, confirms a certain dose-efficacy relation, although conclusive evidence of a linear relationship is not provided.

In view of these results, the 500-mg tablet used in the Phase III multicentre trial in France, appears to be the most appropriate dose to achieve complete therapeutic response in a single dose regimen.

This efficacy is confirmed in the Phase III trials conducted in a large number of patients. Clinical cure rates of at least 40% are achieved in the first few days of treatment, subsequently increasing to 80%. Mycologic cure occurs in more than 80% of cases. This difference is due to the strict criteria for clinical cure. Both asymptomatic patients with positive culture and symptomatic patients with negative culture are considered as treatment failures.

The choice of reference compounds is important. Both clotrimazole and miconazole are approved topical agents which have been widely used in the United States since the 1980s. In comparative clinical trials lasting 10–14 days, both clotrimazole and miconazole demonstrated excellent efficacy, achieving higher cure rates than nystatin (70–80%). This excellent efficacy is

maintained even in treatment periods of less than 14 days, which is that recommended for nystatin. Table 1 summarizes the efficacy results of some published clinical trials [24].

Sertaconazole was not found to be less efficacious than the reference treatments in any of the trials, neither in terms of statistical significance nor appreciable difference. In general, few patients abandoned due to lack of efficacy.

Another noteworthy factor is that clinical and mycological efficacy were maintained over time. The number of relapses due to treatment therapy was low and in one of the studies was significantly less than with the control compound (econazole). However, the period of time established to determine relapse in one of the studies was relatively short (7 days) whilst in another of the studies it was 14 days. In the multicentre trial carried out in France this period was 4 weeks. All the studies, therefore, included adequate time periods (7–14 days) for the evaluation of clinical and mycological efficacy and somewhat inferior to those recommended (4–6 weeks) for the determi-

Table 1  
Trials in vaginitis

Design	Drug/dose/duration	Complete cure <sup>a</sup>	Mycologic cure	Author
Double blind, randomized, multicentre	Clotrimazole 500 mg (×1)	75% (63–87)	79% (68–91)	Fleury et al., 1985 [33]
	Clotrimazole 200 mg (×3)	71% (58–84)	74% (62–87)	
Open, randomized	Clotrimazole 500 mg (×1)	–	82% (75–90)	Loendersloot et al., 1985 [35]
	Clotrimazole 100 mg (×6)	–	85% (77–92)	
Non-comparative, multicentre	Clotrimazole 500 mg (×1)	–	87% (80–94)	Goorsmans et al., 1982 [34]
	–	–	–	
Open, randomized, multicentre	Miconazole 2% (×14)	69% (53–84)	74% (60–89)	Pasquale et al., 1979 [36]
	Miconazole 2% (×7)	79% (67–91)	88% (79–98)	
Randomized, multicentre	Terconazole 0.4% (×7)	71% (65–77)	–	Corson et al., 1991 [23]
	Terconazole 0.8% (×7)	72% (66–77)	–	
	Miconazole 2% (×7)	68% (61–74)	–	
Randomized, double-blind	Terconazole 80 mg (×3)	40% (0–83)	–	Thomason et al., 1990 [37]
	Miconazole 2% (×7)	67% (36–97)	–	
	Placebo (×7)	11% (0–32)	–	
Double-blind randomized, multicentre	Placebo (×3)(×6)	23% (13–32)	37% (25–48)	Brown et al., 1986 [32]
	Butoconazole 2% (×3)	52% (42–62)	63% (53–73)	
	Butoconazole 2% (×6)	58% (48–68)	79% (71–88)	
	Miconazole 2% (×6)	54% (44–64)	72% (62–81)	

<sup>a</sup>Numbers in brackets: 95% C.I.

nation of recurrences. Significant differences between treatments were only observed in the study with a longer follow-up period which implies a certain superiority for sertaconazole. With shorter follow up periods, these differences cannot be determined. Further studies are needed to confirm this favorable finding for sertaconazole. The efficacy variables chosen are appropriate considering those published in the literature and those recommended in *General Guidelines for the Clinical Evaluation of Anti-infective Drug Products* [25] issued by specialized organizations (Infectious Disease Society of America and Food and Drug Administration).

#### 4.3.2. Safety

A total of 1478 women participated in the clinical trials described in this review, 768 of whom had received different formulations of vaginal sertaconazole. A wide range of methods were used in these studies to determine safety: structured and unstructured methods for reporting adverse events, gynecological examination, blood tests, plasma and urine analysis to rule out systemic absorption and tests on vital signs.

None of the patients treated with sertaconazole needed to be withdrawn from the study due to intolerability or adverse reactions, whilst two patients treated with miconazole and clotrimazole did.

The local tolerability of sertaconazole administered by the vaginal route was good. Few local adverse events were reported, approximately 3–5% less than those reported with the reference compounds. The large majority of local adverse events were mild or moderate and did not require treatment. Causality was difficult to establish due to co-existing symptoms (pruritus, burning, pain, erythema and edema). Pruritus and burning were mainly reported which are typical of this type of drug and reflect the therapeutic efficacy of the treatment. This type of local reaction, especially pruritus, is frequent especially in the first few days of antimycotic treatment (1–6%) and is a reaction to antigens released due to fungal cytotoxicity [26].

Systemic tolerability was very satisfactory in all trials and the adverse events reported did not

have a causal relationship with the study drug. No clinically important alterations were observed in laboratory parameters, which confirms the absence of systemic absorption. Data obtained in the clinical trials reviewed appear to be appropriate as they are in agreement with those that appear in the literature, therefore validating the assertions expressed. Topical antimycotics generally present a good safety profile with few systemic adverse effects. Only 0.2% of patients reported headache or abdominal discomfort, although in some studies (e.g. with terconazole) the incidence of systemic adverse effects reached 10% (Corson et al. [23]); therefore, the pharmacological safety of sertaconazole is noteworthy.

Topical antimycotic treatment with sertaconazole may be recommended as therapy of choice in vulvovaginal candidiasis since, although oral drugs are efficacious and well accepted by patients, they need to be used with caution due to their potential adverse effects (gastrointestinal, hepatotoxicity), some of them rare although serious (angioedema, Stevens–Johnson syndrome) and interactions with other drugs [27–29].

In general, sertaconazole by the vaginal route is well tolerated and has a high safety profile when used in patients or healthy volunteers. In view of these data no contraindications or special cautions are required. Compared to alternative drugs, there appears to be a certain tendency towards fewer local adverse events and better patient acceptance of the dosage forms (more than 90% consider them to be satisfactory or very satisfactory).

The usual contraindications for this class of drugs (e.g. hypersensitivity to azole derivatives or excipients of the formulation) should be given, also the lack of studies in children, women over 70 years old, pregnant women breast feeding women or immunocompromised patients should be pointed out.

## 5. Conclusions in gynecology

### 5.1. Justification for therapy

Vulvovaginal candidiasis is an inflammatory

process which affects the vulva and/or vagina, caused by superficial infection of the epithelia cells by *Candida* sp. It is the second most common form of vaginitis in the United States, second only to bacterial vaginosis [30] and is estimated to be the reason for visits to doctors in 20–25% of cases of vaginitis. In the last few years an increase in prescriptions for treatment has been observed and it is estimated that 75% of women will experience at least one episode of vaginal infection by *Candida* during the course of their lives and of these 40–45% will suffer at least one recurrence. Although both acute and recurrent vulvovaginitis are not life-threatening diseases, the discomfort and distress suffered by these patients have a considerable effect on their quality of life [31]; therefore, research into new treatments that are both efficacious and safe is required.

The object of this report is the evaluation of sertaconazole, a new broad spectrum antimycotic for vaginal application both as a single dose of a 500-mg tablet, 2% cream or ovule monodosis, 300 mg, in the treatment of vulvovaginal candidiasis.

The clinical trials were performed in Phase I centers and hospitals in Spain. A supplementary study was carried out in France.

### 5.2. Efficacy

Sertaconazole by this route of administration, and in all vaginal pharmaceutical forms, has proven to be efficacious in patients with vulvovaginal candidiasis. Its clinical efficacy has been supported by objective parameters (microscopy) and it has a high microbiological eradication on culture test. It is comparable with standard topical antimycotics (clotrimazole, miconazole, econazole) and, using internationally accepted evaluation parameters, there is a tendency towards superiority in clinical and mycological aspects, although this does not reach statistical significance.

### 5.3. Safety

This vaginally administered drug has demonstrated safety, and no serious or unexpected ad-

verse events have been reported. The lack of systemic absorption is corroborated by the non-existence of systemic drug-related adverse effects and the fact that no alterations in laboratory tests or vital signs have been found. Compared with alternative topical antifungal drugs, there appears to be fewer local adverse events, which makes it considerably safer than oral treatment.

Contraindications for this drug are the usual ones for topical antimycotics. The lack of data on children, the elderly, pregnant or breast-feeding women should also be pointed out.

### 5.4. Proposed dose regimen

The recommended pharmaceutical forms and doses are a single dose 500-mg tablet, a single dose 300 mg sustained release ovule and 2% vaginal cream applied once a day.

### 5.5. Benefit / risk ratio

In view of its lack of systemic absorption, the level of drug concentrations observed in vaginal secretion, its rate of action, its short and long term efficacy, its excellent local and systemic tolerability and patient acceptance, sertaconazole has a favorable benefit/risk ratio and all these properties clearly support its use in the treatment of vulvovaginal candidiasis.

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